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REVIEW

# Unproven Therapies for Diabetes and Their Implications

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## ABSTRACT

Diabetes is a chronic disease and is one of the leading causes of morbidity and mortality worldwide. Being an ancient disease, many individuals follow complementary and alternative medicinal (CAM) therapies for either the cure or prevention of the disease. The popularity of these practices among the general public is in no way a testimony to their safety and efficacy. Due to the possibility of undesirable interactions with conventional medicines, it is imperative that patients are asked about CAM use during patient assessment. Patient- and physician-targeted awareness programs on various aspects of CAM use must be initiated to create a better understanding of evidence-based use of these practices. In addition, there should be guidelines in place based on clinical trial outcomes, and stricter regulations need to be enforced on CAM practices to ensure their safety and effectiveness.

**Keywords:** Ayurveda; CAM; Complementary and alternative medicine; Diabetes; Herbal medicine; Supplements; TM; Traditional medicine

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# INTRODUCTION

## Worldwide Prevalence of Diabetes

The World Health Organization (WHO) defines diabetes as a serious chronic disease that manifests either when the pancreas does not produce enough insulin (a hormone that regulates blood glucose) or when the body cannot effectively use the insulin it produces [1]. Diabetes, if not managed, can damage many organs of the body such as the kidneys, heart, eyes, blood vessels, and nerves. As per International Diabetes Federation (IDF) statistics, about 415 million adults were afflicted with the disease in 2015, and this number is estimated to be 642 million by the year 2040. It also estimated that more than half a million children aged 14 and under are affected with type 1 diabetes mellitus (T1DM) [2]. Diabetes accounts for one death every 6 s, and the number of deaths caused by diabetes is 5 million, a figure much higher than those caused by HIV (1.5 million), tuberculosis (1.5 million), and malaria (0.6 million) combined [2, 3].

With advances in modern medicine, a dramatic improvement in life expectancy was achieved after 1940. As per the WHO, the average life span of a child born in 2015 is predicted to be 71.4 years, whereas earlier estimates of global life expectancy were 30.9 years in 1900, 46.7 in 1940, and 61.13 in 1980. [4, 5]. Diabetes being a disease that accounts for a huge economic burden as well as physical and mental disability, all patients should have the privilege of receiving effective therapies with the fewest adverse effects. Special precautions must be undertaken while managing elderly patients because of the interplay among different factors such as age, genetics, lifestyle, and physiological conditions that are known to aggravate the disease. In an earlier review, we discussed in detail the pathophysiology of diabetes in the elderly and the necessity for individualized care and proven therapies to prevent disability in advancing age [6].

## History of Diabetes

Diabetes is an ancient disease that was known to physicians more than 3500 years ago. The Ebers Papyrus, considered the greatest Egyptian medical document, describes diabetes as a condition of “too great emptying of the urine” [7, 8]. Indian physicians around the same time observed that the urine of individuals with diabetes attracted ants and flies. They referred to it as “madhumeha” or “honey urine” and also noted that these patients suffered from extreme thirst and foul breath (likely due to ketosis). Conditions such as polyuria and glycosuria were also documented by physicians of that time [8–10]. The first ever scientific remedy, the discovery of insulin, was developed in 1922, winning its discoverers the Nobel Prize in 1923 [11], whereas the first ever oral scientific remedy, sulphonylurea, was not available until the 1950s. Hence the physicians, prior to the discovery of these modern medicines, had no other choice than to use locally available indigenous medicines. In the current scenario, depending on the type of diabetes and its etiology, patients may be treated with either an oral drug or injectable or a combination of both. In T1DM with absolute insulin deficiency, insulin pump therapy or multiple daily insulin injections are the only therapeutic modalities, in the absence of which subjects are likely to die.

## Diabetes-Related Complications

Diabetes burdens different organ systems, and therefore subjects with diabetes have a greater risk of developing serious health complications. Acute complications such as diabetic

ketoacidosis (resulting from insulin deficiency) and coma (resulting from hypoglycemia) often result in the death of the individual. Chronic elevation of blood glucose levels presents with vascular complications, either microvascular (neuropathy, nephropathy, retinopathy) or macrovascular (cardiovascular disease, stroke, peripheral vascular disease) in nature. Peripheral vascular disease often results in hard to heal bruises or injuries and gangrene, which may finally require amputations [12, 13]. Dementia [14], depression [15], and sexual dysfunction [16, 17] have also often been found to be associated with diabetes.

### CAM Therapy and Popularity

Many patients resort to complementary and alternative medicinal (CAM) practices at least once during their lifetime. 'Complementary' therapies are those that are used together with conventional treatment, whereas 'alternative' therapies are used in place of conventional treatment. The National Center for Complementary and Alternative Medicine (NCCAM), now renamed the National Center for Complementary and Integrative Health (NCCIH), is a subsidiary of the National Institutes of Health (NIH), USA, and refers to CAM as those healthcare approaches developed outside of the realm of conventional medicine. Complementary and alternative health approaches fall into one of two subgroups, viz., natural products and mind and body practices. Natural products (widely available and often sold as dietary supplements) consist of herbs (or botanicals), vitamins and minerals, and probiotics. Mind and body practices include a variety of procedures or techniques administered or taught by a trained practitioner or teacher (e.g., yoga, chiropractic and osteopathic manipulation, meditation, massage therapy, acupuncture, relaxation techniques, tai chi, etc.) [18].

The 2012 National Health Interview Survey revealed that about 33% of adults used complementary approaches, and natural products were found to be favored by 17% of adults and about 5% of children. In spite of having a comprehensive health insurance program, 59 million Americans have willingly spent a total of about 30 billion dollars on complementary health approaches [19, 20]. Another study from Israel reported that almost every fourth patient with diabetes uses CAM [21]. Dissatisfaction arising from conventional therapies, at times, and higher treatment expenses, concern about the side effects of drugs, desire to have a grip on the course of the disease, and a notion that CAM therapies are compatible with patient values and beliefs [22–25] are some of the reasons why many choose CAM over conventional therapies. Considering this widespread popularity of various CAM practices, in this review we have made an effort to recapitulate their pros and cons pertaining to diabetes treatment.

### Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

## IMPLICATIONS OF CAM THERAPY FOR DIABETES TREATMENT

### Frequently Used CAM Therapies for Diabetes

Individuals with diabetes, cancer, and hypertension are found to be the predominant followers of CAM as compared to their healthy

counterparts [26]. Individuals with diabetes tend to use CAM therapies mostly to complement conventional therapy and resort to nutritional advice or lifestyle diets, herbal remedies, massage therapy, spiritual healing, and meditation training [26, 27]. Of the CAM therapies, those most popularly used and studied for diabetes treatment are herbs, dietary supplements, and mind-body medicine [28]. This is not surprising as many of them are widely available and inexpensive and are inherent in peoples' cultures and ancestral beliefs. An investigation using ethnographic methods was carried out on an urban population of Kerala to understand the usage of complementary therapies in managing type 2 diabetes mellitus (T2DM). The study pointed out that patients' perceptions of a disease and its management are largely based on their cultural background and environmental resources. Many of them frequently use Ayurvedic and traditional herbal medicines as supplements to conventional therapy [29]. An overview of natural products generally used for diabetes management is depicted in Table 1 (herbs) and Table 2 (dietary supplements).

## Impact of CAM Therapies in Diabetes Treatment Outcome

The American Diabetes Association's Standards of Medical Care do not support the use of vitamin, mineral, or herbal supplements for diabetes management because of the lack of sufficient evidence [30]. Several systematic reviews have been published that assess the impact and efficacy of various CAM therapies on preventing and treating diabetes. Recently, the effect of Ayurveda on treating diabetes mellitus was studied by Sridharan et al., and the effect of Chinese herbal medicines on impaired glucose tolerance or impaired fasting blood glucose was assessed by Grant et al. Both of these reviews pointed out the benefits of following these traditional systems of medicine in treating diabetes or pre-diabetic conditions. The authors, however, stop short of recommending such practices, citing the biased nature of certain studies and lack of sufficient evidence [31, 32].

The popularity of these practices generally stems from patient's expectations of their efficacy [33] as well as being associated with advanced stages of the disease [34]. Some investigations into the psycho-social impacts of CAM practices have tried to evaluate the expectations and perceptions regarding their efficacy. In a study that included cancer patients, for many their expectations of positive CAM effects were not met [34]. In a survey conducted among participants in the SEARCH for Diabetes in Youth, patients who followed a 'CAM diet' reported a better quality of life (QOL), whereas supplement use and stress reduction activities resulted in decreased QOL. Besides, children who did not follow any CAM practices experienced fewer treatment barriers [35]. A similar trend was also reported by another study, where higher CAM use in fact correlated with a decreased quality of life in people with T2DM and/or cardiovascular disease. This was attributed to the negative effects of using multiple therapies because some of them could in fact interfere with conventional care [36].

CAM users were also found to show decreased adherence to prescribed medications. They become both logistically and psychologically burdened and may need to discontinue part or all of their prescribed diabetes medications to be able to continue using CAM [37]. CAM therapies, depending on the amount or type, can help or harm patients and often cause adverse responses, which

**Table 1** Commonly used herbs to treat diabetes

| Name | Active constituents | Beneficial effects/ hypothesized mechanism of action | Side effects/drug interactions and contradictions | References |
|---|---|---|---|---|
| Bitter melon (*Momordica charantia*) | Momordin, charantin, polypeptide P, vicine | Hypoglycemic action, insulin mimetic, enhances glucose uptake by tissues, inhibition of glucose producing enzymes, enhances glucose oxidation (G6PDH pathway) | Gastrointestinal discomfort, hypoglycemic coma, favism, hemolytic anemia in persons with G-6PDH deficiency, abortifacient activity of α and β momorcharin, hypoglycemia when used with sulfonylureas | [28, 117] |
| Fenugreek (*Trigonella foenum-graecum*) | Saponins, glycosides<br>Seeds contain: alkaloids, 4-hydroxyisoleucine, fenugreekine | Insulin secretagog, hypoglycemic activity, lipid-lowering effects, increase HDL cholesterol, Slows carbohydrate absorption and delays gastric emptying, inhibits glucose transport, increases insulin receptors, improves utilization of peripheral glucose | Diarrhea, gas, uterine contractions, allergic reactions, drug interaction with hypoglycemic agents, anticoagulant drugs, MAO inhibitors, contraindicated in pregnancy | [27, 117] |
| *Panex ginseng, P. quiquefolius* (Ginseng) | Ginsenosides | Insulin mimetic, hypoglycemic action, enhances psycho-physiological performance, stimulates immune system, may decrease carbohydrate absorption in portal circulation, may increase glucose transport and uptake, may modulate insulin secretion, alters hepatic glucose metabolism | Estrogenic effect with breast tenderness, amenorrhea, vaginal bleeding and impotence, hypertension, insomnia, interacts with anticoagulant and antiplatelet medications; hypoglycemic agents; corticosteroids; oral contraceptives; digoxin; MAO inhibitors and tricyclic antidepressants; diuretics | [27, 28, 118] |

**Table 1** continued

| Name | Active constituents | Beneficial effects/ hypothesized mechanism of action | Side effects/drug interactions and contradictions | References |
|---|---|---|---|---|
| Ginkgo (*Ginkgo biloba*) | Flavonoids (ginkgo-flavone glycosides), terpenoids (ginkgolides and bilobalides) | Inhibit the platelet-activating factor, useful in cerebrovascular insufficiency and peripheral vascular disease, antioxidant, neuroprotective | Transient headaches, cross allergenicity with poison ivy, interacts with anticoagulants, SSRI, MAO inhibitors | [27, 52, 119] |
| *Aloe vera* | Glucomannan | Fiber may promote glucose uptake, pharmacokinetic interaction (CYP3A4), pharmacodynamic interaction (enhancement in adipose tissue insulin signaling pathway) | Abdominal pain, laxative component induces diarrhea, additive hypoglycemia if combined with secretagogs, drug interactions with sevoflurane, pioglitazone, repaglinide | [28, 52, 117, 120] |
| *Cinnamomum zeylanicum* | Compound similar to procyanidin type-A polymers, coumarins | Increases insulin sensitivity by increasing PPAR (alpha and gamma) expression, increases cellular glucose entry by enhanced insulin receptor phosphorylation and translocation of GLUT4 glucose transporter to the plasma membrane, promotes glycogen synthesis | Skin irritations if used topically, interacts with secretagogs and cause hypoglycemia, coumarins possess anticoagulant, carcinogenic, and hepatotoxic properties | [117, 121] |
| *Gymnema sylvestre* | Gymnemosides, saponins, stigmasterol, and amino acid derivatives (e.g., betaine, choline, and trimethylamine) | Insulin secretagog, increases glucose uptake promoting enzymes, stimulates and increase beta cell number | May cause hypoglycemia when combined with secretagogs | [28, 117] |

**Table 1** continued

| Name | Active constituents | Beneficial effects/ hypothesized mechanism of action | Side effects/drug interactions and contradictions | References |
|---|---|---|---|---|
| *Opuntia streptacantha* (Nopal) | Mucopolysaccharide<br>Fibers, pectin | Slow carbohydrate and lipid absorption, possibly increases insulin sensitivity | Diarrhea, nausea, abdominal fullness, increases stool volume, drug interaction—improved blood glucose and insulin with sulfonylureas (without hypoglycemia) | [52, 117] |
| *Coccinia indica* (ivy gourd) | Pectin, triterpenes | Insulin mimetic, hypoglycemic activity, helps lower elevated levels of glucose-6-phosphatase and lactase dehydrogenase | Allergenic plant components may cause hypoglycemia when combined with secretagogs | [52, 121] |

indirectly lead to other diseases. Diabetic patients frequently undergo treatment for associated diseases such as hypertension, neuropathy, cardiovascular disease, and so on. While evaluating the effect of CAMs, it is important to understand drugs and drug interactions in depth, and failure to record a patient's present history of CAM use may lead to problems with other prescribed medicines [38, 39].

## CAM THERAPY: DRAWBACKS AND COMPLICATIONS

CAM practices pose general risks such as the patient being overloaded with consecutive unsuccessful therapeutic measures owing to false diagnoses, developing life-threatening situations and adverse effects, and hidden costs of treatment [40, 41].

Unlike conventional drugs, CAM products, especially herbal medicines and supplements, are complex mixtures of bioactive entities with varying degrees of therapeutic effects. The chemical constitutions of some products vary based on the season, growing conditions, plant part used for extraction, and so on [42, 43]. High variability in levels of ginsenosides in ginseng across different source parameters, viz., ginseng type (batch, preparation, variety, and species), assay technique, and ginsenoside type in turn caused high variability in their efficacy as revealed in a meta-analysis. This is an indication that the reported safety and efficacy data of a particular product may differ greatly when compared to other over-the-counter batches, preparations, varieties, and species of the herb [44]. The complex nature of the products along with poorly regulated manufacturing processes often makes it

**Table 2** Commonly used dietary supplements to treat diabetes

| Name | Beneficial effects/hypothesized mechanism of action | Side effects/potential drug interactions and contradictions | References |
|---|---|---|---|
| Chromium | Lipid-lowering effects, insulin-sensitizing effect by decreasing tyrosine phosphatase activity or direct effect on insulin receptor by increasing tyrosine kinase activity at the insulin receptor may promote glucose transport | Renal toxicity and dermatological reactions, potential hypoglycemia with secretagogs, steroids may decrease chromium levels, vitamin C may increase chromium absorption | [27, 52, 117] |
| Omega-3 fatty acid/fish oil | Lowers triglycerides, antiinflammatory, antiplatelet, hypotensive, slight increase in blood glucose | High intake might cause bleeding, fish meat to be eaten with caution because of contamination with high levels of methyl mercury; may increase LDL, drug interactions with anticoagulant and antihypertension drugs | [27, 28] |
| Alpha-lipoic acid | Improves insulin resistance and increase glucose effectiveness | Can affect thyroid function in patients with thyroid disease, might produce allergic skin reactions, abdominal pain, nausea, vomiting, diarrhea, and vertigo | [28, 52, 122] |
| Coenzyme Q10 | Improvement in pain and paraesthesia in diabetic neuropathy | No effect on blood glucose, additive effects with antihypertensive drugs | [21, 28, 52] |
| Magnesium | Insulin secretagog, essential in glucose metabolism, prevent diabetic complications, increased insulin sensitivity | Diarrhea, abdominal cramping, magnesium toxicity in individuals with renal failure, antibiotics, drug interactions with drugs to prevent osteoporosis, calcium channel blockers, muscle relaxants, diuretics | [27, 28] |
| Zinc | Improves insulin levels, lipid-lowering effects, improves weight loss, metalloenzyme activitor | Nausea, vomiting, reduce absorption of folic acid, tetracyclines and copper, reduce the effect of therapies that rely on dopamine receptor antagonists | [27, 120] |
| Vanadium | Insulin mimetic, increase insulin sensitivity | Prolonged high doses may cause renal toxicity, gastrointestinal upset | [28, 52] |

difficult to determine possible drug interactions [42].

## Complications from Drug Interactions

Co-administration of herbal medicines or supplements along with conventional therapies is a common practice among patients with diabetes. A possibility of drug interactions with these products exists, which can alter the pharmacokinetics or pharmacodynamics of conventional drugs, resulting in potential side effects [42, 45]. In case of pharmacokinetic interactions,

co-administered herbs or supplements may alter the absorption, distribution, metabolism, and/or excretion of conventional drugs. Such interactions can induce and inhibit intestinal and hepatic metabolic enzymes (e.g., CYP enzymes) as well as drug transporters and efflux proteins. For instance, any modulating activity of these herbal remedies on CYP function can greatly influence the bioavailability of conventional drugs [42]. In pharmacodynamic interactions, herbal remedies may interact with the same target molecules leading to synergistic or antagonistic herb-drug interactions. Synergistic effects can cause toxicity and complicate the dosing regimens of medications, whereas antagonistic interactions often lead to decreased efficacy and failure of therapy [42, 46].

Owing to the long-term nature of therapies for patients with diabetes, the consequences of these drug interactions can be fatal. Herbs possessing hypoglycemic activity, such as ginseng, garlic, and bitter melon, are all reported to have additive effects in patients taking oral hypoglycemics or insulin [44, 47–49]. In contrast, dietary gums (e.g., gum guar), usually prescribed to overcome postprandial hyperglycemia, were found to reduce the absorption of hypoglycemic agents such as metformin and glibenclamide because of their effect on prolonging gastric retention [48, 50, 51]. A list of some other possible drug interactions reported by earlier investigations or reviews can be found in Tables 1 and 2.

## CHALLENGES TO USING CAM THERAPIES

### Compromised Quality of CAM Products

Lack of proper adherence to manufacturing, marketing, and storage protocols can lead to deterioration of the product quality, viz., contamination with other substances, intra- and inter-product variations, mislabeling of the contents, and so on, thereby leaving us unsure regarding their safety and efficacy [41, 52, 53]. A large percentage of Ayurvedic medicines, both US- and Indian-manufactured, available over the Internet was found to contain lead, mercury, or arsenic, much above their acceptable levels [54], and several studies have reported serious consequences for patients using 'herbal' products that contained 'hidden' active drug compounds or heavy metal contaminants [55–59]. Lead intoxication from the use of Ayurvedic medications has been reported among pregnant women by the Centers for Disease Control and Prevention (CDC), USA [60]. Several Indian herbal medicines were also found to cause lead toxicity in patients with diabetes [61–63]. Some Indian herbal products claiming to be antidiabetic were even reported to be contaminated with hypoglycemic agents such as glibenclamide [64]. Since 2007, the FDA has imposed an import alert on certain Ayurvedic products to prevent such products from entering the USA [65]. Reviewers who undertook a systematic study of Ayurvedic drugs to treat diabetes agree upon a few things. These studies are laden with major methodological limitations such as few randomized trials, underpowered studies, and inappropriate statistical methods, all questioning the credibility of such preparations [32, 66, 67].

Chinese proprietary medicines are no exception, for instance, an antidiabetic preparation marketed as 'wonder pills' contained phenformin, a banned substance [68]. In some cases, toxic herbal constituents became part of the preparation inadvertently. "Chinese herb nephropathy" is a classic example: the herb *Stephania tetrandra*, supposed to be included in weight-reduction

pills, was substituted with a nephrotoxic herb, *Aristolochia fangchi*, causing nephropathy and/or cancer. Unintended use of *Aristolochia fangchi* in women attending a slimming clinic in Belgium resulted in one-third of them requiring a renal transplant, and some of the others developed carcinomas [69–71].

### Concerns with Other CAM Practices

Other CAM practices are also not free from side effects. Therapies involving mechanical techniques might cause detrimental effects. Chiropractors, for example, applying controlled force to a spinal joint can cause vertebral arterial dissection after upper spinal manipulation [72]. Acupuncture (stimulating specific points on the body by inserting thin needles through the skin) can cause complications such as pneumothorax [73, 74], cardiac tamponade [75–77], and central nervous system injuries [78]. Serious infectious complications (such as hepatitis, HIV, sub-acute bacterial endocarditis, etc.) can also arise when the practitioners do not follow aseptic techniques [79, 80]. Discontinuing conventional treatment for acupuncture therapy recently led to the death of a 30-year-old T1DM patient from India [81]. Another peculiar diabetes treatment practiced in Kerala is "sweet therapy," which claims to stimulate the sleeping pancreas to secrete insulin with the intake of glucose-rich foods such as sweet deserts. However, the long-term serious implications of such modalities on the health of the patients are not documented. Mind-body therapies, which involve movements (yoga, tai-chi, etc.) can at best be considered alternative modes of exercise [82, 83]. They may impart changes in the behavior and psychology of patients, thereby helping them to cope with the disease and increase the overall quality of life [84]. However, neither yoga [85, 86] nor tai-chi [87–89] has been shown to have any significant impact on improving the glycemic status.

### Lack of Proper Communication With Health Practitioners

CAM practitioners usually do not encourage inquiries regarding the constituents of their preparations, and most patients are not very interested in knowing this as they consider such preparations to be 'natural' or 'safe.' Healthcare professionals are mostly unaware of CAM use by their patients and are not consulted prior to their use [90]. All of these factors make it difficult to know whether CAM therapy has played any significant contributory role in the efficacy or failure of a conventional treatment [91].

In its Position Statement on "Unproven Therapies," the ADA raises the concern that most patients do not admit the use of alternative medicine and therefore care providers need to specifically ask their patients about them. The ADA continuously evaluates the effectiveness, potential risk to patients, and so on to characterize the effectiveness of such treatment modalities. They however do not recommend the use of any of these unless their safety and efficacy have been established by current standards [92].

## REGULATORY STATUS OF CAM THERAPIES

### Regulations on CAM Products

Many countries including the USA do not have a comprehensive policy or an authority responsible for CAM and traditional medicine (TM) practices. In the USA, national non-governmental organizations, such as the

Accreditation Commission for Acupuncture and Oriental Medicine, the American Board of Medical Acupuncture, the Council of Chiropractic Education, and so on, accredit education in some of them, while most other nations do not have these [93]. The Dietary Supplement Health and Education Act (DSHEA 1994) of the US government went on to define the term "dietary supplement," effectively taking out any product containing a vitamin, mineral, herb, or amino acid marketed as a supplement to the normal diet from obtaining USFDA approval for their safety and efficacy, thus leading to their sales even in grocery stores [41, 94].

Only 25 of the WHO's 191 countries have a national policy on TM/CAM, and only 64 countries regulate herbal medicines [95]. In view of this, the WHO published the "Regulatory Situation of Herbal Medicines: a Worldwide Review" with the sole aim of assisting its members in the development of policies and regulations [96]. In India, the Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homoeopathy) was formed in November 2014 by elevation of The Department of AYUSH, with a view to providing focused attention on the development of education and research in these disciplines. The Government of India imposed Good Manufacturing Practices (GMP) under the Drug and Cosmetics Act, 1940, to ensure and enhance the quality of alternative medicines (ASU: Ayurveda, Unani, and Siddha) and also set up a Standards Setting cum Drug Testing Laboratory (Pharmacopoeial Laboratory for Indian Medicine) specifically for these systems of medicine [97]. However, Ayurvedic medicines "prepared in same way as mentioned in ancient Ayurvedic treatises" have been waived from rigorous pharmacological and toxicological studies by rule [98], and products claiming this tend to be widely available to the general public, thereby raising questions regarding their purity, safety, and efficacy. Measures such as these can only hamper the efforts toward control, education, research, and self-regulation.

### Regulations on CAM Practitioners

Another issue of great concern is that CAM practitioners in many countries are not regulated in any manner. There is no system to evaluate the training or expertise of these practitioners [93, 99–101]. This is a serious concern, especially in rural areas where timely access to treatment (government or private) is an issue, as these local practitioners become the primary point of approach and may end up as a hindrance to better treatment options [93, 101]. In many cases, alternative medicine is widely promoted among the public with claims that it is highly effective and supposedly devoid of side effects [98]. 'The Drugs and Magic Remedies (Objectionable Advertisements) Act,' 1954, by the Indian Parliament controls the advertising of drugs in India, restricting advertisements for such 'wonder drugs or remedies' to some extent [102]. Restricting CAM practitioners without any acceptable educational qualifications and adopting standards of practice will be the next appropriate step toward minimizing practice risks [103].

## RECOMMENDATIONS FOR PROSPECTIVE CAM USE

### Systematically Controlled Clinical Trials

Many antidiabetic drugs used in modern medicine have a natural origin [104], and administering them in their natural form may

not be of much benefit. Metformin, a popular antidiabetic drug, is derived from a traditional antidiabetic plant, *Galega officinalis* (Goat's Rue or French Lilac) [105], whose active ingredient was found to be galegine or isoamylene guanidine. While guanidine and certain derivatives were found to have toxic effects, the biguanides (two linked guanidine rings) turned out to be beneficial and have been available for therapeutic use since the 1950s. Twenty years later, two of them (phenformin and buformin) were withdrawn because of side effects such as frequent lactic acidosis and increased cardiac mortality. However, a less lipophilic biguanide, metformin, turned out to be safe and was approved for use in the USA in 1995 [106]. Phlorizin, isolated from the bark of apple trees, was found to cause glycosuria [107], but later led to the discovery of better analogs such as dapagliflozin, empagliflozin, and canagliflozin [108]. Exenatide, a glucagon-like peptide-1 (GLP-1) agonist, is a synthetic version of exendin-4, a hormone found in the venom of the Gila monster *Heloderma suspectum* [109, 110]. The alpha-glucosidase inhibitor used in T2DM, acarbose, is a pseudo-oligosaccharide isolated from the culture broths of various actinomycetes [111]. With regulated research there is a higher probability that many more natural agents can be used in modern medicine after controlled clinical trials.

Randomized clinical trials of herbal medicine interventions most often underreport the crucial characteristics of the intervention thereby deviating from the standards set by Consolidated Standards of Reporting Trials (CONSORT). CONSORT specifies the necessary information to be included while reporting controlled clinical trials of any intervention including herbal medicines [112, 113]. Experts also recommend that CAM and dietary supplements should be subject to scrutiny similar to conventional medicines by organizations such as the NIH and FDA. Any measure to bypass these may render the healthcare system inefficient, incapable, and dangerous [114, 115].

### Proper Patient Counseling

As more patients with diabetes resort to CAM therapies, modern healthcare practitioners need to be aware of these practices and be prepared to counsel such patients, when needed, about the available options. They should be able to assess as well as present information to the patients regarding the expected risks, side effects, benefits, and choices regarding self-management and the cost to the patient, helping them to make an informed choice [28, 116]. For individuals exploring supplements, FDA documents such as, "Tips for the savvy supplement user," "Tips for older dietary supplement users," "questions and answers on dietary supplements," and so on, might be helpful (accessible at http://www.fda.gov).

## CONCLUSIONS

Age-old systems of alternate medications may be effective for a number of illnesses. However, for a very serious illness like diabetes with multiple long-term complications including, but not limited to, renal and hepatic dysfunction, it is always wiser to follow scientifically studied and proven remedies with known drug interactions and with data on their safety and efficacy in different age groups. CAM practices need to be brought under a regulatory framework and assessed to gain insights into issues concerning their efficacy and safety,

which will eventually generate faith in these indigenous systems of medicine.

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